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Cumulative irritancy comparison of adapalene gel 0.1% versus other retinoid products when applied in combination with topical antimicrobial agents

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This randomized, investigator-blinded study evaluated the level of skin tolerance to adapalene gel 0.1%, tretinoin cream 0.025%, or tretinoin microsphere gel 0.1% when applied in combination with clindamycin phosphate lotion 1%, erythromycin gel 2%, benzoyl peroxide gel 5%, or erythromycin-benzoyl peroxide gel. A total of 37 subjects underwent daily application of the topical antimicrobial and retinoid products to sites on their upper back under protective patches for approximately 16 hours each day; Friday patches were left in place over the weekend. Testing continued daily for 3 weeks or until discontinuation caused by a severe adverse reaction to any of the test products or to the patch. Adapalene gel 0.1% demonstrated statistically significantly ($P < .001$) less irritation after repeated application under occlusive conditions than tretinoin cream 0.025% or tretinoin microsphere gel 0.1%. Moreover, the application of adapalene gel 0.1% under these conditions, concomitantly with various antimicrobial agents, was safe and well tolerated in this subject population. In view of its low irritation potential and its efficacy, adapalene gel 0.1%, in combination with antimicrobial agents should be considered for the treatment of acne vulgaris. (J Am Acad Dermatol 2003;49:S227-32.)

Although combination therapy with a retinoid and an antimicrobial agent is efficacious in the treatment of acne,[1-4] irritation associated with the use of multiple topical agents can have an impact on patient compliance. The irritation potential of tretinoin and isotretinoin is a limiting factor to their widespread use and obliges the patient to follow unusual dosing regimens to avoid symptoms of "tretinoin dermatitis."[5,6] Potential side effects of tretinoin therapy include peeling, burning, erythema, and pustular flare, an exacerbation of inflammatory acne lesions shortly after initiation of therapy.[7] Irritation can also occur with antibiotic use. Typical adverse reactions include itching, dryness, peeling, and erythema; however, these are mostly minor.

The vehicle of a topical formulation, whether lotion, ointment, cream, or gel, affects absorption of the therapeutic agent and can influence the efficacy and tolerability of the formulation. Most formulations are emulsions of oils, water, and alcohols in varying proportions. These nontherapeutic agents can themselves be irritating or cause allergic reactions in some patients. Selection of the least irritating vehicle formulation with the lowest appropriate starting dose minimizes irritation with topical retinoids.[8]

Extensive clinical studies have been carried out to evaluate the irritancy of topical antimicrobial agents and topical retinoids alone. In addition, a 21-day patch test study has shown that adapalene can be coadministered with benzoyl peroxide, clindamycin and erythromycin with little or no evidence of irritancy compared to significantly higher levels reported with similar tretinoin combinations.[9] This study investigated the level of epidermal tolerance to the combined application of adapalene gel 0.1% versus tretinoin cream 0.025% and tretinoin micro-

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sphere gel 0.1%, with 1 of 4 antimicrobial agents (clindamycin phosphate lotion 1%, erythromycin gel 2%, benzoyl peroxide gel 5%, and erythromycin-benzoyl peroxide gel). The assessment method was a modified version of the 21-day cumulative irritancy assay (patch test), a well-accepted method[10] designed to assess the irritation potential of topically applied materials. This type of assay measures irritation caused by direct damage to epidermal cells, rather than to any immunologic (allergic) mechanism.[11]

SUBJECTS AND METHODS

Subjects

A total of 37 healthy subjects, men and women over the age of 18 years, were enrolled in the study. Any skin phototype was accepted providing the degree of skin pigmentation did not interfere with test site evaluation. All female subjects underwent 2 pregnancy tests (1 before and 1 after the study), with the exception of those who were menopausal or who had undergone a hysterectomy, bilateral tubal ligation or bilateral ovariectomy. Subjects who were pregnant or breast-feeding were excluded from the study, as were those with abnormal skin hyperpigmentation, a history of skin disease that could confound site analysis (eg, atopic dermatitis, eczema, or psoriasis) or known sensitivity to skin-care products, topical drugs, latex, or any other specific kind of tape. Subjects with scars, moles, sunburns, or other blemishes on the test area that would interfere with grading were also excluded from the study. Use of any topical drug on the application area within 1 week before beginning the protocol, or any systemic drug that may have affected the irritation within 2 weeks before study onset, or any systemic retinoid that may have increased the irritation reaction within 3 months before study onset were not permitted.

Methods

The study was conducted as an independent, single-center, randomized, controlled, investigator/evaluator-blinded, intraindividual comparison involving healthy subjects meeting specified inclusion criteria. All subjects started in the study on the same day and were randomized to receive 4 topical antimicrobial products (clindamycin phosphate lotion 1%, erythromycin gel 2%, benzoyl peroxide gel 5%, and erythromycin-benzoyl peroxide gel) and 3 topical retinoid products (adapalene gel 0.1%, tretinoin cream 0.025% and tretinoin microsphere gel 0.1%) for a period of 3 weeks. The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and Good Clinical Practice guidelines, and in compliance with local regulatory requirements. The study protocol was reviewed and approved by an Institutional Review Board. All subjects provided their written informed consent before entering the study.

Study procedures

At screening, demographic profiles and medical histories were recorded for all eligible subjects and a pregnancy test was conducted in females of childbearing potential. On a daily basis, the 4 antimicrobial products were randomly applied under protective patches to the upper area of the back of each subject. Approximately 0.5 mL of each antimicrobial product was applied to a separate 2- × 7.5-cm area in the morning of each treatment day. Each antimicrobial product was consistently applied to the same area in all subjects throughout the trial. Eight hours later, each of the antimicrobial treatment zones was subdivided into 3 test areas with dimensions of 2 × 2.5 cm. Approximately 0.2 g of each retinoid product was randomly applied under occlusive conditions to the antimicrobial test areas and left in place overnight (about 16 hours). This procedure was repeated daily on Mondays through Fridays for 3 weeks. The Friday evening applications were left in place until the following Monday morning (about 64 hours).

Irritancy assessment

The subject's backs were photographed, by a trained evaluator, prior to the assessment of skin reactions on the patch test areas before each evening's application of test products. Erythema was graded on a scale of none (0), barely visible (0.5), mild (1), moderate (2), or severe (3). The following cutaneous reactions occurring at test sites were also noted: edema; development of papules or pustules; development of vesiculation or blisters; hyper-pigmentation; weeping/oozing; spreading of reaction beyond the test site; and marked reaction to the adhesive patch.

Open questions were posed to the subjects daily to elicit information regarding adverse events and concomitant medication. Product application was discontinued at a site when an irritation reaction related to the product was rated as grade 3 for any site. When an irritation reaction caused by adhesivity of the patch prohibited patching at a particular site, all sites on the subject were discontinued.

Irritancy evaluation

The principal irritancy criterion was the cumulative irritancy index (CII)[10,11] assessed by clinical evaluation of erythema on test sites. Sites were scored at baseline (day 1) and at each visit (days 2-5, 8-12, 15-19 and 22) immediately before test patch application. The CII was calculated for each of 12 treatment combinations and each subject with the equation:

$$\text{CII} = \text{sum of irritation scores}/21$$

Irritation scores for each treatment combination were graded as described above, ranging from 0 to 3. Baseline scores at day 1 were excluded from the calculation. Subjects who missed an isolated day's reading were assigned a score for that visit equal to that from the following day's reading. Scores for Saturday and Sunday were assigned the value of the following Monday's reading. When the product application was discontinued at 1 or more sites for any form of severe intolerance, a score of 3 was imputed for the remaining readings. Subjects who missed more than 1 reading were withdrawn from the study.

Individual CII scores were averaged across subjects to obtain a mean CII for each treatment. Mean CII was plotted against time for each antimicrobial product separately. Erythema scores and other local reactions were plotted by time period in frequency tables when applicable.

Statistical analyses

CII scores were submitted to a mixed model analysis of variance with random effect for subject, and fixed effects for antimicrobial product, retinoid product and antimicrobial-retinoid interaction. In the absence of a significant interaction ($P > .05$) the retinoid products were compared pairwise with respect to CII using the Tukey multiple comparison test, performed at the 1% and 5% significance levels. In addition, separate analyses were performed for each antimicrobial product, using an appropriately reduced linear model (random subject and fixed test product).

RESULTS

Disposition of subjects

Of the 37 subjects enrolled, 33 (89%) completed the study. One subject was lost to follow-up, and 3 discontinued at their request for reasons unrelated to treatment.

Demographic and baseline characteristics

There were more women (28 subjects; 76%) than men (9 subjects; 24%) in the study (Table I). The mean age was 52 years (range 19-75). Most subjects were white (86%); most of the remainder were Hispanic (11%). The largest proportion of subjects had skin phototype III (49%). Roughly equal proportions of subjects were distributed among the other skin phototypes I, II, IV, and V (11% to 13%).

Irritancy evaluation

The identity of the antimicrobial product statistically significantly influenced the irritancy potential of the 3 retinoid products. Clindamycin lotion combinations yielded the lowest irritancy scores (Fig 1).

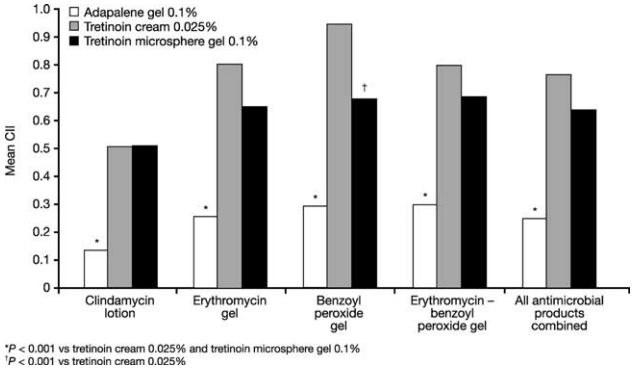

Fig 1. Mean CII for each antimicrobial product and for all antimicrobial products combined: comparison between retinoid products.

Table I. Demographic distribution of subjects

Variable	Number (%) of subjects
Age (years)	
Mean ± SD	52 ± 16.5
Range	19-75
Gender	
Male	9 (24)
Female	28 (76)
Race	
White	32 (86)
Hispanic	4 (11)
Mixed/Other	1 (3)
Skin phototype	
I	4 (11)
II	5 (13)
III	18 (49)
IV	5 (13)
V	5 (13)

Adapalene gel 0.1% was statistically significantly less irritating than either of the tretinoin formulations, when applied with each of the 4 antimicrobial products ($P < .001$; Fig 1). This was true for the combined analysis and in the separate analysis of each antimicrobial product.

The 2 tretinoin formulations were not always equally irritating: their mean CII scores were similar for application with clindamycin lotion (0.50 for the 0.025% cream; 0.51 for the 0.1% microsphere gel); however, for all other antimicrobial products the 0.025% cream was more irritating than the 0.1% microsphere gel. This difference in irritation potential between the 2 tretinoin formulations reached statistical significance for the combination with benzoyl peroxide gel (mean CII scores of 0.95 for the 0.025% cream vs 0.68 for the 0.1% microsphere gel; $P < .001$). Fig 2 shows the evolution of mean CII scores for each antimicrobial-retinoid product com-

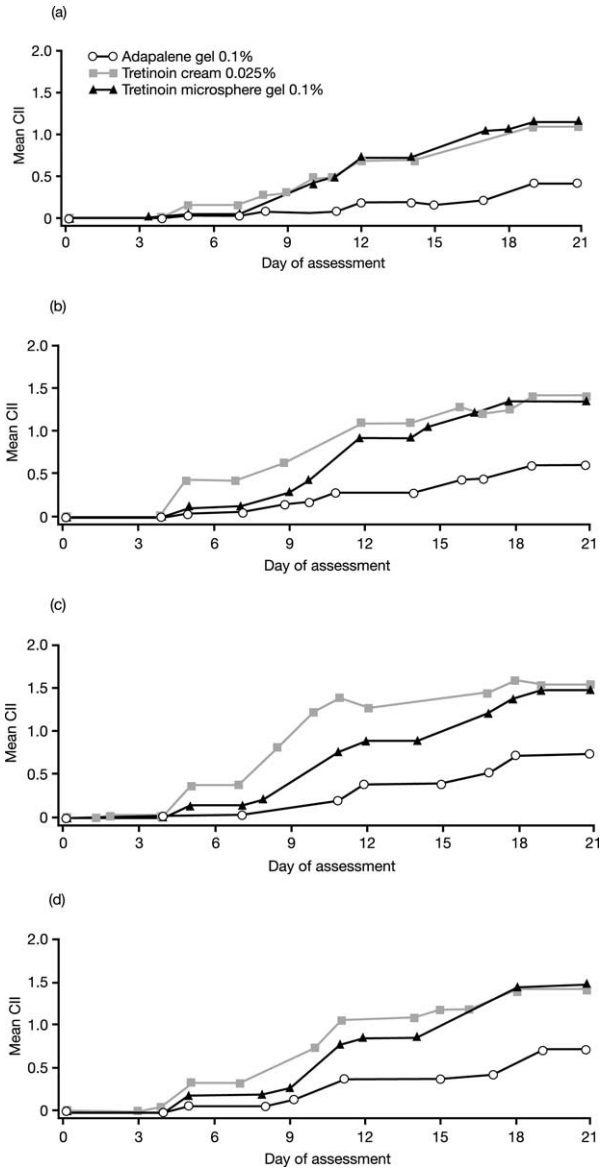

Fig 2. Daily evolution of mean CII scores for each antimicrobial-retinoid combination separately. **(a)** Clindamycin lotion; **(b)** erythromycin gel; **(c)** benzoyl peroxide gel; and **(d)** erythromycin-benzoyl peroxide gel.

bination. Fig 3 shows the irritancy of all antimicrobial/retinoid products when applied to a typical subject's back.

Safety evaluation

There were no serious adverse events. Four subjects (11%) experienced a total of 11 treatment-related adverse events. These (occurrence of severe erythema; irritation score ≥3) resulted in the discontinuation of further patch applications at that site. Only 1 subject experienced severe erythema at a site treated with adapalene gel 0.1% in combination with erythromycin gel. The remaining severe application

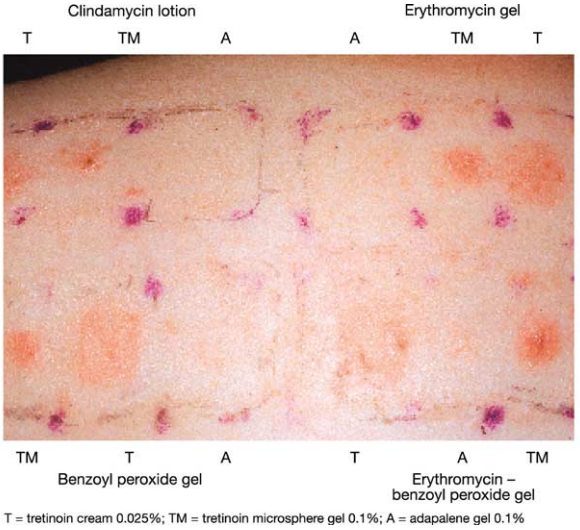

Fig 3. Typical irritation response. Four large zones correspond to areas of application of each antimicrobial product. Each zone is subdivided into 3 sites on which retinoid products were applied in a randomized order.

site reactions that required discontinuation involved the use of the tretinoin formulations: 4 with tretinoin cream 0.025% and 6 with tretinoin microsphere gel 0.1%. No discontinuation of patch application occurred on sites treated with clindamycin lotion.

DISCUSSION

This study was designed to compare the irritancy potential of 3 retinoid formulations (adapalene gel 0.1%, tretinoin cream 0.025% and tretinoin microsphere gel 0.1%) when applied concomitantly with 4 antimicrobial agents to the skin of healthy adults. Irritancy was assessed with the 21-day cumulative irritancy assay (patch test).[10,11]

Adapalene gel 0.1% was statistically significantly less irritating than either tretinoin formulation when applied in combination with any of the 4 antimicrobial products. Irritation scores for all 3 retinoids were considerably lower with clindamycin lotion than with any other antimicrobial product. The effect of clindamycin lotion in reducing retinoid irritancy has been observed previously.[1] Tretinoin microsphere gel 0.1% was statistically significantly less irritating than tretinoin cream 0.025% when applied concomitantly with benzoyl peroxide gel. However, with the other 3 antimicrobial products, there was no significant difference in irritancy between the 2 tretinoin products. In 1 case, erythema with an irritation score of grade 3 (severe) was experienced as a result of the application of adapalene gel 0.1%, compared with 4 such events with tretinoin cream 0.025% and 6 with tretinoin microsphere gel 0.1%. The results of this study suggest that adapalene gel 0.1% may have

a lower rate of adverse events associated with its use under actual therapeutic conditions. Because other studies have demonstrated comparable efficacy of adapalene to retinoids in the treatment of acne vulgaris,[12] the suggestion of a reduced safety risk may have clinical significance.

Cumulative irritation to adapalene gel 0.1% was slower than to the tretinoin formulations, with adapalene-treated areas showing noticeably less irritation after 5 to 8 days (Fig 2). The 0.1% microsphere gel formulation delayed the onset of irritation to tretinoin compared with the 0.025% cream, but did not reduce cumulative irritation. Over days 5 to 16, mean daily CII values for the tretinoin formulations differed considerably for all antimicrobial products except clindamycin lotion, although final day mean scores were almost identical for all 4 antimicrobial products. The difference in mean CII values between tretinoin formulations was only statistically significant with benzoyl peroxide gel when averaged across the whole test period (Fig 1).

The antiinflammatory effect of adapalene is believed to contribute to its tolerability profile.[13] Adapalene gel 0.1% and cream 0.1% do not induce epidermal hyperplasia, which appears to be a result of nonspecific irritant activity of all-*trans* retinoic acid,[14,15] or a pharmacologic effect. Adapalene gel 0.1% has a low skin irritation potential even when applied immediately after washing, a procedure contrary to physicians' recommendations for other retinoids to avoid "tretinoin dermatitis."[16]

Adapalene gel 0.1% was also found to be much better tolerated than any of 6 tretinoin formulations, including 2 gels (0.01% and 0.025%), 3 creams (0.025%, 0.05% and 0.1%) and a microsphere formulation (0.1% gel).[17] In several studies comparing adapalene aqueous gel 0.1% with tretinoin gel 0.025% cutaneous tolerability was greater for adapalene.[18-23] The superior tolerability of adapalene compared with tretinoin is further confirmed by this study.

The complementary and additive mechanisms of action of retinoids and antimicrobials are a highly effective approach for the treatment of acne vulgaris in most patients. Controlled clinical trials have shown combined therapy to have significantly greater efficacy than the individual therapies administered alone.[1-4] However, the potential for irritation must be considered alongside its efficacy. Chronic or acute irritation resulting from acne therapy may result in patient dissatisfaction and withdrawal from treatment. The lower irritation potential of adapalene gel 0.1%, as shown in this study, in combination with its demonstrated efficacy,[18-20] indicates that it is a good choice as therapy in combination with antimicrobial agents for the treatment of mild to moderate acne vulgaris.

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